IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: CROSSMAN, A., *et al*	EXAMINER: JAVANMARD, S.
SERIAL NO.: 10/527,761	ART UNIT: 1627
FILED: MARCH 10, 2005	CONFIRMATION NO.: 3221
TITLE: TREATMENT OF DYSKINESIA	

VIA EFS
Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RULE 132 DECLARATION

Dear Examiner Javanmard,

1. My name is Erwan Bezard, Ph.D.

2. I am Director of the "Institut des Maladies Neurogeneratives" at INSERM (CNRS Neurodegenerative Disorders Institute) and have authored or co-authored over 120 professional publications in the field of neurobiology, primarily focused on Parkinson's disease and related disorders. My research interests include the study of compensatory mechanisms, levodopa-induced dyskinesia, the basic pathophysiology of basal ganglia circuitry, and the development of new strategies to alleviate symptoms and/or slow disease progression. My Curriculum Vitae ("Biographical Sketch") is attached hereto.

3. In preparing to sign this Declaration, I have read the above-referenced application and reviewed the claims in their present form. I understand that claims 14-15, 19, and 25-27 are rejected as unpatentable over (obvious in view of) Chenard (EP 0900568 A2) in view of Skradski (*Epilepsia* 2000) in further view of Dursun (*Canadian Journal of Psychiatry* 2000). It is my further understanding that the Examiner contends that it would have been obvious at the time of the invention to employ an AMPA receptor antagonist as a treatment for dyskinesia as allegedly taught by Chenard and, specifically, to employ topiramate. The latter is apparently based on the Examiner's belief that Skradski teaches that topiramate is an AMPA receptor

antagonist, and that one could reasonably expect that the treatment of dyskinesia with one AMPA receptor antagonist over another would be equally successful.

4. With regard to Skradski, it is my view that topiramate was not believed to be an AMPA receptor antagonist at the time of the instant application's filing and, thus, topiramate would not be considered in the context of Chenard's broad use statements.

5. As detailed in the Office Action Response filed prior to this Declaration (specifically, on May 26, 2010), Skradski is inconclusive about the antagonistic effect of topiramate (TPM) "on some types of...AMPA...and/or kainate receptors.". Indeed, Skradski described the results of his study as follows: "This precludes any definitive conclusions about the particular receptor subtype blocked by TPM..." and "Ongoing studies to identify the molecular site through which TPM exerts its effects on kainate-evoked currents will undoubtedly provide important information concerning...the mechanism of action of TPM..." My reading of Skradski at the time of filing would not have left me with any expectation, let alone any reasonable expectation, that topiramate exerts an antagonistic effect on AMPA receptors.

6. In fact, at the time the above-referenced application was filed (indeed, throughout the late 1990s and early 2000s), topiramate was generally considered to act as a kainite receptor antagonist and not as an AMPA receptor antagonist.

7. I note that the Office Action Response filed prior to this Declaration (specifically, on May 26, 2010) provided an example of this belief in the form of Gryder (2003 *J Neuroscience* 23(18):7069-7074). Gryder, submitted herewith, reports on their investigation of the actions of topiramate on pharmacologically isolated synaptic responses mediated by AMPA and GluR5 kainate receptors. Gryder not only emphasized the inconclusiveness of Skradski -- "...it was not possible in these studies to distinguish between the effects of topiramate on these" (AMPA and kainate) "two receptor types." – but also itself concluded that topiramate selectively blocks the kainate receptor (last sentence of introduction, as well as "This indicates that GluR5 kainate receptors are likely to be substantially blocked during topiramate therapy at clinically effective doses.").

8. It is my understanding that the Examiner has pointed to a statement in Gryder noting a very weak depressant action of topiramate on synaptic responses predominantly mediated by AMPA receptors. At the time of filing, however, a person in this field of research would have relied on Gryder's repeated statements regarding topiramate's selective inhibition of

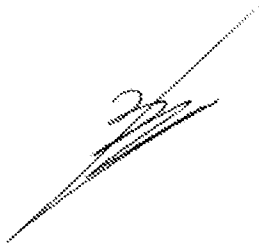
the component of the excitatory synaptic response in BLA principal neurons that is mediated by pharmacologically defined GluR5 kainate receptors, rather than a single statement regarding weak depressant action. Furthermore, Gryder emphasizes that AMPA receptors are crucial for excitatory synaptic transmission throughout the CNS, that the blockade of AMPA receptors would have been expected to produce dramatic neurobehavioral impairment, and that this did not occur with topiramate at therapeutic doses.

9. It would appear to me that the Examiner is reading Skradski to now fit the claimed inventive effect, rather than reading the publication as it would have been read and interpreted by the person of ordinary skill in the art at the time of filing.

10. Having reviewed both publications, and being very well versed with the state of the art at the time of filing, I maintain that a person in the field would have felt no reasonable inclination to choose topiramate as an AMPA receptor antagonist, since it was widely believed to be a kainate receptor antagonist, and not an AMPA receptor antagonist

11. Thus, I believe topiramate would not have been considered an AMPA receptor antagonist at the time of filing, let alone an AMPA receptor antagonist to be considered in the context of Chenard's broad treatment statements.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Date: September 15, 2010

By: Erwan Bezard, Ph.D.
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